Retinopathy in Ischemic Stroke Subtypes

Fergus N. Doubal, MRCP; Baljean Dhillon, FRCOphth; Martin S. Dennis, MD; Joanna M. Wardlaw, MD

Background and Purpose—Lacunar stroke is associated with an intrinsic cerebral small vessel disorder of unknown etiology, although possible causes include increased blood–brain barrier permeability. Retinal arterioles are similar to cerebral small vessels and retinopathy occurs secondary to increased blood–retinal barrier permeability. We hypothesized that there would be higher rates of retinopathy in patients with acute lacunar versus cortical stroke.

Methods—We prospectively recruited patients presenting with acute lacunar and cortical ischemic stroke. An experienced stroke physician diagnosed and subtyped the stroke based on clinical features and cerebral MRI. We performed 6 dilated digital retinal photographs of each eye in all patients. A carefully trained physician graded retinopathy (one or more of hard or soft exudates, microaneurysms, or hemorrhages) blind to stroke type as definitely present/absent or uncertain.

Results—We recruited 220 patients; 6 were excluded with ungradeable photographs leaving 214 patients for analysis (105 lacunar and 109 cortical strokes). Mean age was 68 years (SD, 11 years) and median National Institutes of Health Stroke Scale 2. Similar proportions of each group had diabetes (17% lacunar versus 10% cortical) and hypertension (56% lacunar and 66% cortical). Eighteen percent of lacunar and 19% of cortical patients had any retinopathy. After adjusting for baseline differences in age, hypertension, and diabetes, retinopathy was not associated with ischemic stroke subtype.

Conclusions—We have not demonstrated a strong association between retinopathy and ischemic stroke subtype. However, larger samples or assessment of other retinal vascular abnormalities may yield positive associations. (Stroke. 2009;40:389-393.)

Key Words: etiology ■ lacunar stroke ■ retinopathy

Although accounting for 25% of all ischemic stroke,1 the exact etiology of lacunar stroke remains unknown.2 Lacunar strokes are thought to arise from disease in a single perforating artery causing small, deep cerebral lesions. Possible mechanisms include local large or small vessel atheroma, vasospasm, and microemboli blocking these arteries. Conventional causes of stroke probably account for only 15% to 20% of lacunar strokes, suggesting other mechanisms may be responsible in the majority.2 More recently, it has been suggested that disordered small vessel endothelium or blood–brain barrier dysfunction may contribute.3,4 The retinal and cerebral small vessels are developmentally related, are of similar size, and share physiological characteristics. The blood–retinal barrier is analogous to the blood–brain barrier.5 Large population studies show associations between retinopathy (defined as the presence of hard or soft exudates, hemorrhage, or microaneurysms) and previous as well as future stroke risk.6–9 Retinopathy is associated with increased permeability of the blood–retinal barrier10 and we therefore hypothesized that there could be higher rates of retinopathy in patients with acute ischemic lacunar stroke compared with acute ischemic cortical stroke controls in which the mechanism is largely atherothromboembolic.

Patients and Methods
We recruited patients prospectively with acute clinical lacunar or mild cortical ischemic stroke from our hospital stroke service, which serves a largely urban population of approximately 400,000 people. We included patients who presented up to 3 months after symptom onset who had a definite diagnosis of stroke and who could provide informed consent. We excluded patients with severe total anterior circulation stroke (because the atherothromboembolic disease mechanisms responsible for severe cortical stroke are present in patients with milder cortical stroke) or who were medically unstable, had contraindications to MRI, or who were unwilling to participate. The hospital sees approximately 550 patients with possible stroke a year of whom 250 might have been eligible with a lacunar or mild cortical stroke and the study ran for 2.5 years. We used a control group of patients with cortical ischemic stroke to control for having a stroke, risk factor profiles, and secondary stroke prevention medications (as opposed to normal age-matched controls, which would not have controlled for any of these factors). All patients were examined by an

Received June 20, 2008; final revision received June 30, 2008; accepted July 8, 2008.
From the Division of Clinical Neurosciences (F.N.D., M.S.D., J.M.W.) and the Princess Alexandra Eye Pavilion (B.D.), University of Edinburgh, Edinburgh, UK.
Correspondence to F.N. Doubal, Division of Clinical Neurosciences, Bramwell Dott Building, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. E-mail fergus.doubal@ed.ac.uk
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.529388

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experienced stroke physician and classified initially into lacunar or cortical stroke clinical syndromes according to the Oxfordshire Community Stroke Project classification. Patients had diagnostic cerebral MRI (including diffusion-weighted imaging) at presentation to identify the site of the recent infarct and quantify white matter hyperintensities. All scanning was performed on a 1.5-T MR scanner (Signa LX; General Electric) with 22 mT/m maximum-strength gradients. Diagnostic MRI also included axial T2-weighted, fluid-attenuated inversion recovery and gradient echo sequences (details available on request). All patients underwent usual investigations for stroke (carotid Doppler ultrasound, electrocardiogram, blood tests, and other tests if indicated). We recorded age, gender, National Institutes of Health Stroke Scale (NIHSS),12 presence of atrial fibrillation, history of diabetes, hypertension, ischemic heart disease, peripheral vascular disease, and previous stroke/transient ischemic attack. All patients had 6-field retinal photography (centered on the disc, macula, lateral macula, nasal to the disc, upper arcade and lower arcade) of the left and right eyes with 1% tropicamide eye drops where possible using a Canon CR-DGi digital retinal camera (Canon USA Inc).

Mild cortical stroke syndrome was defined as maximum clinical deficit of either weakness or sensory loss in the face, arm, or leg or loss of higher cerebral dysfunction (eg, dysphasia or neglect) or weakness in more than one limb in the presence of loss of higher cerebral function equivalent to a partial anterior circulation stroke syndrome or homonymous hemianopia suggestive of occipital cortical infarct. Lacunar stroke syndrome was defined as one of the classical lacunar syndromes (eg, pure motor weakness and/or sensory loss of face and arm, arm and leg, or all 3, ataxic hemiparesis, or clumsy hand dysarthria syndrome).11 After initial clinical classification, we further classified stroke subtype using radiological criteria (ie, whether the recent infarct on MRI was cortical or lacunar) and used both the clinical and radiological classification to assign the final stroke subtype classification. Where the clinical classification differed from the radiological classification, the radiological classification was used as cortical syndromes can arise from lacunar strokes and vice versa. If no definite recent lesion was visible on the scan, the clinical classification was used. No patients had concurrent acute lacunar and cortical infarcts. If a patient had old lesions present, we recorded their presence and type (infarct/hemorrhage and cortical/lacunar) but subtyped based on the acute lesion. The study was approved by the local research ethics committee and all patients gave written informed consent.

Image Analysis
All MRI scans were coded by an experienced neuroradiologist (J.W.) for the presence, location, and size of the recent symptomatic infarcts and any old infarcts or hemorrhages. A recent infarct was defined as a hyperintense area on diffusion imaging (with corresponding reduced signal on the apparent diffusion coefficient image) with or without increased signal on fluid-attenuated inversion recovery or T2-weighted imaging in a distribution compatible with an arterial territory. Lacunar infarcts were in the cerebral hemispheric white matter, basal ganglia, or brainstem and <2 cm diameter if recent (lesions >2 cm were classed as striatocapsular/cortical because they have large artery disease causes). Retinal photographs were graded by a single trained physician (F.D.) for retinopathy (defined as the presence of hemorrhage, microaneurysms or hard or soft exudates) in either eye as being absent, questionably present, or present according to an established, validated proforma13 blind to clinical details. Training was performed using standard test images and with ophthalmologists performing regular diabetic screening. All lesions identified using previously defined criteria14 that were questionably present or present were checked by a consultant ophthalmologist (B.D.). The intrarater repeatability kappa score for the presence versus absence of retinopathy (for 30 randomly chosen cases in this study) was 0.84 (excellent). This technique was based on a retinopathy grading scale (microaneurysms and hemorrhages) with a published intrarater kappa score of 0.9.15

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lacunar Stroke</th>
<th>Cortical Stroke</th>
<th>P Value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>105</td>
<td>109</td>
<td>···</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>66.3 (11.6)</td>
<td>70.6 (11.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>60 (57%)</td>
<td>74 (68%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>3</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>4 (4%)</td>
<td>15 (14%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Medical history of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>18 (17%)</td>
<td>11 (10%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>14 (13%)</td>
<td>32 (29%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>59 (56%)</td>
<td>62 (66%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Transient ischemic attack, n (%)</td>
<td>16 (15%)</td>
<td>13 (12%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>9 (9%)</td>
<td>12 (11%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Old infarct on MRI, n (%)</td>
<td>35 (33%)</td>
<td>38 (35%)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*Statistical test used: mean age (2-sample t test), median NIHSS (Mann-Whitney U test), peripheral vascular disease, and atrial fibrillation (Fisher exact test); all others χ2 test for association.

Statistical Analysis
We used 2-sample t tests, Fisher exact test, and χ2 test for association to investigate baseline characteristics between the lacunar and cortical groups and associations with retinopathy and multiple binary logistic regression to assess multivariate effects of explanatory variables. All analysis was performed with Minitab software (Version 14; Minitab Inc). Sample size calculation based on existing literature on retinal findings in stroke suggested that 197 patients would be needed to detect a difference of prevalence in retinopathy of 10% with 80% power at the 0.05 significance level.

Results
We recruited 220 patients of whom 6 were excluded with photographs of inadequate quality (due to cataract, poor compliance, and inadequate dilatation) to assess retinopathy leaving 214 patients for analysis. The mean age was 68.4 years (SD, 11.6 years), 62% were male, and the median NIHSS was 2. There were 109 patients with acute cortical stroke and 105 with acute lacunar stroke. Acute stroke lesions were seen on MRI (diffusion-weighted imaging and/or T2/fluid-attenuated inversion recovery based on signal characteristics and lack of focal atrophy) in 159 of 214 (74%) patients of whom 144 of 214 (67%) of the cohort had diffusion-weighted imaging-positive lesions (the rate reflecting the small nature of the lesions and occasional delays to scanning). Consistent with previous studies,16 38 of 214 (18%) patients had their stroke subtype classification changed by MRI findings from cortical to lacunar or vice versa. Seventy-three of 214 patients had old infarcts on imaging; in 16, the old infarct was of a different subtype as opposed to the acute lesion and 4 had both old cortical and lacunar infarcts.

The baseline characteristics of the lacunar and cortical groups are shown in Table 1. The cortical patients were older than the patients with lacunar stroke (mean, 70.6 years versus 66.3 years; 2-sample t test estimate of difference, 4.25; 95% CI, 1.15 to 7.34 years; P = 0.007) with lower NIHSS (median,
Table 3. Multivariable Analysis of Associations With Retinopathy for All 214 Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable OR for Association with Retinopathy</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar stroke subtype</td>
<td>0.76</td>
<td>0.37–1.57</td>
<td>0.46</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.95–1.01</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.82</td>
<td>0.80–1.75</td>
<td>0.61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.02</td>
<td>1.24–7.34</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*All ORs are corrected for the other variables in the table.

2 versus 3 Mann-Whitney U test; \( P<0.01 \) and had higher rates of atrial fibrillation (14% versus 4%, \( P=0.009 \)) and ischemic heart disease (29% versus 13%, \( P=0.004 \)). There were no significant differences between the 2 groups in gender or rates of hypertension, diabetes, or peripheral vascular disease.

Of 214 patients, 40 patients (18.7%) had retinopathy present: 19 of 105 patients (18%) with lacunar stroke and 21 of 109 patients (19%) with cortical stroke had retinopathy (\( \chi^2 \) statistic 0.48, \( P=0.8 \). Table 2 shows individual components of retinopathy by stroke subtype. There were no significant differences between individual components of retinopathy and stroke subtype.

With univariable analysis, only the presence of diabetes was associated with retinopathy (\( \chi^2 \) statistic 4.8, \( P=0.028 \)) but not age, NIHSS, hypertension, diabetes, ischemic heart disease, peripheral vascular disease, previous transient ischemic attack/stroke, or atrial fibrillation. After correcting for mild baseline differences in age, hypertension, and diabetes with multivariable binary logistic regression, there was no association between ischemic stroke subtype and presence of retinopathy (OR, 0.76; 95% CI, 0.37 to 1.57; \( P=0.46 \); see Table 3). The only variable independently associated with the presence of retinopathy after correction for age, stroke subtype, and hypertension was diabetes (OR, 3.02%; 95% CI, 1.24 to 7.34; \( P=0.01 \)). To examine possible effect modifiers, we assessed all 2-way interactions (among age, hypertension, diabetes, and stroke subtype) and sequentially removed those interactions contributing least to the model where their effect was nonsignificant. After this process, the only significant interaction that remained was between hypertension and age in predicting retinopathy (OR for a combined age multiplied by the presence of hypertension explanatory variable of 0.94; 95% CI, 0.88 to 1.00; \( P=0.04 \)) when modeled with age, hypertension, diabetes, and stroke subtype, but this did not significantly alter the associations shown in Table 3.

To ensure accurate ischemic stroke classification, we performed a prespecified subgroup analysis excluding patients who had an old lesion of a different type to the acute stroke classification, eg, a patient presenting with an acute lacunar stroke who had an old cortical lesion. Multivariable logistic regression correcting for age, diabetes, and hypertension in these 194 patients did not change the size, direction, and significance of the results in Table 3.

Discussion

We have not demonstrated an association between ischemic stroke subtype and the presence of any retinopathy. In this study, the only variable that was associated with retinopathy on multivariable analyses was diabetes.

The strengths of the study are that stroke was diagnosed by an expert at the time of the stroke, all patients had diagnostic MRI at presentation to permit accurate diagnosis and subtyping, we used a prespecified clinical and imaging based hierarchy to classify stroke subtype, and our sample size exceeded our original calculated estimate that would be required to detect a 10% difference between stroke subtypes. We can therefore be reasonably confident that we have not missed an important difference in retinopathy prevalence simply through inadequate study design. Furthermore, all patients had retinal photography performed at the time of the stroke and no previous studies have compared retinopathy in ischemic stroke subtypes. The limitations are that the cross-sectional design means that we can only report on associations between retinopathy and stroke. There were modest imbalances in baseline variables, which may not have been completely corrected with multivariate analyses. Although we recruited beyond the number indicated in our sample size calculation, more patients would be needed to show differences in overall prevalence of less than 10% or in specific subtypes of retinopathy. Fluorescein angiography may have demonstrated subclinical differences in microvascular perfusion between stroke subtypes, however, is more invasive than color fundus photography and therefore would have restricted recruitment and was not feasible in this study. The study sample size was perhaps limited by exclusion of patients with severe strokes (equivalent to total anterior circulation strokes) and the need for patients to have a definite diagnosis of stroke rather than a possible diagnosis of stroke. However, retinal photography would have been difficult in severely unwell patients (the subject needs to sit up, hold their head still, and follow commands) and the atherothromboembolic disease mechanisms present in severe cortical strokes will be represented in the included milder cortical strokes. We subtyped acute ischemic stroke into lacunar and cortical stroke using the Oxfordshire Community Stroke Project classification modified by the results of the brain MRI and therefore unbiased by using risk factors to classify stroke (eg, like in...
the Trial of Org 10172 in Acute Stroke Treatment classification). This study focused on patients with acute clinically proven strokes; however, some patients had old lesions on their MRI scans that may or may not have represented clinical strokes (most appeared not to; we did not ascertain a history of clinically evident stroke in 65 of 73 patients with old infarcts). We repeated the analysis excluding the few patients who had an old lesion type that differed from the acute ischemic type and this sensitivity analysis did not change the main results shown in Table 3.

How does our study relate to previous information on retinopathy and stroke? In the large population-based Atherosclerosis Risk in Communities (ARIC) study, the presence of any retinopathy predicted future ischemic stroke during 3.5 years follow-up with a relative risk of 2.58 (95% CI, 1.59 to 4.20) corrected for diabetes, hypertension, age, and other vascular risk factors. A similar finding is reported for diabetic subjects with a longer follow-up from the same study. Furthermore, baseline retinopathy in the Blue Mountains Eye Study was reported as being significantly associated with future risk of stroke and transient ischemic attack with a relative risk of 1.7 (95% CI, 1.0 to 2.8). Although demonstrating a link between retinopathy and future stroke in general, none of these studies reported or compared associations with different subtypes of ischemic stroke. The evidence for an association between retinopathy and history of stroke is less compelling (perhaps reflecting the inherent difficulties in obtaining accurate medical histories); the Cardiovascular Health Study reported that retinopathy was associated with a clinical history of stroke (OR, 2.0; 95% CI, 1.1 to 3.6) but not with MRI defined cerebral infarction of an unspecified subtype (OR, 0.94; 95% CI, 0.63 to 1.41). There have been no published studies thus far that have compared retinopathy between ischemic stroke subtypes.

We demonstrated a prevalence of retinopathy of 19% in patients with mild ischemic stroke and mean age of 68 years. This is slightly higher than population-based prevalences of 7.0% (ARIC) and 8.3% (Cardiovascular Health Study) probably reflecting the fact that the patients in the present study had higher rates of vascular disease than community-dwelling healthy subjects. The prevalence in the present study was slightly lower than in patients with diabetes with ischemic stroke of 33% (ARIC) but similar to that in patients in Cardiovascular Health Study who had a history of ischemic stroke, 16% of whom had retinopathy. These differences may be explained by different rates of diabetes and stroke severity.

What do our results mean? The aim of the present study was to investigate whether there were higher rates of retinopathy in patients with lacunar stroke because this might reflect blood–retinal barrier breakdown. There is growing evidence that cerebral small vessel disease may be associated with dysfunctional blood–brain barrier and retinal imaging offers an excellent noninvasive method of studying blood vessels that are similar to cerebral vessels. That the rates of retinopathy do not differ between acute ischemic stroke subtypes may be due to several reasons other than our hypothesis being incorrect. One of the first stages in the development of diabetic retinopathy is subtle breakdown of the blood–retinal barrier, which eventually leads to characteristic retinopathy (visible on techniques like fluorescein angiography). In the present study, we have looked at any retinopathy (hemorrhage, exudates, and microaneurysms). Perhaps only certain retinopathic components are associated with blood–retinal barrier leak, whereas others reflect other pathological processes. Although we have reported the findings, this study was not powered to identify differences in individual retinopathy features, only in any retinopathy. Although very similar, it may be that retinal vessels do not behave exactly like cerebral vessels and the changes are too subtle to be identified without retinal fluorescein angiography. Microvascular changes in the brain and the retina may not move in parallel; it is possible that in these patients (with a low NIHSS and stroke severity), the retinal changes may have not yet developed and perhaps studying patients with more severe stroke may have revealed subtype-specific retinopathic differences. Alternatively, it may be that retinopathy is a marker of vascular risk and is coassociated with stroke but not stroke subtypes, because lacunar and cortical strokes have similar hypertension and diabetes risk profiles.9 Future research should perhaps concentrate on carefully subtyping stroke and investigating the use of retinopathy as a marker of risk factor effects on end organs in the individual and how this relates to any future stroke risk.

Acknowledgments

David Perry provided database support.

Sources of Funding

F.N.D. is funded by the Wellcome Trust (075611). The Chief Scientists Office (Scotland) funded the brain imaging (CZB-4-281), which took place in the SFC Brain Imaging Research Centre (www.sbirc.ac.uk). Retinal photographs were taken in the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh. The retinal camera was purchased by the Wellcome Trust (ref 075611).

Disclosures

None.

References


